

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

High interpatient variability of raltegravir CSF concentrations in HIV-positive patients: a pharmacogenetic analysis.

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/140932> since 2016-06-09T15:56:01Z

Published version:

DOI:10.1093/jac/dkt339

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Calcagno A, Cusato J, Simiele M, Motta I, Audagnotto S, Bracchi M, D'Avolio
A, Di Perri G, Bonora S

High interpatient variability of raltegravir CSF concentrations in HIV-positive
patients: a pharmacogenetic analysis.

JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY (2014) 69

DOI: 10.1093/jac/dkt339

The definitive version is available at:

<http://www.jac.oxfordjournals.org/cgi/doi/10.1093/jac/dkt339>

High Interpatient Variability of Raltegravir Cerebrospinal Fluid Concentrations in HIV-positive Patients: a Pharmacogenetic Analysis.

Calcagno Andrea^{*}, Cusato Jessica, Simiele Marco, Motta Ilaria, Audagnotto Sabrina, Bracchi Margherita, D'Avolio Antonio, Di Perri Giovanni and Bonora Stefano.

Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy.

Running Head: Raltegravir PK/PG in the CSF

Type of article: Concise Communication

Key words: antiretroviral; pharmacokinetics; blood brain barrier; p-glycoprotein; hepatic nuclear factor 4 alpha.

Word count: 1760

Corresponding Author:

Andrea Calcagno,
Department of Infectious Diseases, University of Torino
c/o Ospedale Amedeo di Savoia,
C.so Svizzera 164
10159, Torino, Italy
+390114393884, fax +390114393818
andrea.calcagno@unito.it

40 **Objectives:** To analyse the determinants of raltegravir CSF penetration including pharmacogenetics
41 of drug transporters located at the brain-blood-barrier or blood-CSF barrier.

42 **Methods:** Plasma and CSF raltegravir concentrations were determined by a validated High
43 Performance Liquid Chromatography coupled with Mass Spectrometry method in adults on
44 raltegravir-based combination antiretroviral therapy undergoing a lumbar puncture. Single
45 nucleotide polymorphisms in the genes encoding drugs transporters (*ABCB1* 3435, *SLCO1A2*,
46 *ABCC2* and *SLC22A6*) and for the nuclear factor HNF4 α were determined by real-time PCR.

47 **Results:** In 41 patients (73.2% male, 96.3% Caucasians) medianraltegravir plasma and CSF
48 concentrations were 165 ng/mL (83-552) and 31 ng/mL (21-56), respectively. CSF-to-plasma ratios
49 (CPR) ranged from 0.005 to 1.33 [median 0.20, IQR (0.04-0.36)].raltegravir trough CSF
50 concentrations (n=35) correlated withraltegravir plasma levels ($\rho=0.39$, $p=0.019$); CPRs were
51 higher in patients with blood brain barrier damage (0.47 versus 0.18, $p=0.02$). Hepatocyte nuclear
52 factor 4 alpha (HNF4 α) 613 CG genotype carriers had lower trough CSF concentrations (20 versus
53 37 ng/mL, $p=0.03$) and CPRs (0.12 versus 0.27, $p=0.02$). At multivariate linear regression analysis
54 CSF to serum albumin ratio was the only independent predictor ofraltegravir penetration in the CSF.

55 **Conclusions:** Raltegravir penetration into the CSF shows a large inter-patient variability although
56 cerebrospinal fluid concentrations result above wild type IC₅₀ in all patients (and above IC₉₅ in
57 28.6%). In this cohort blood brain barrier permeability is the only independent predictor
58 ofraltegravir CSF to plasma ratio. The impact of single nucleotide polymorphisms in selected genes
59 on raltegravir penetration warrants further studies.

60

61

62

63

64

65

66 **Introduction**

67 Antiretrovirals (ARVs) penetration into the central nervous system (measured as drug
68 concentrations in the cerebrospinal fluid) has been associated with control of HIV replication and to
69 neurocognitive function. Raltegravir (RAL) in combination with other ARVs has been proven to be
70 effective and well-tolerated and to elicit a very fast viral load decay after treatment initiation.¹ Data
71 on raltegravir CSF penetration derives from two papers and a small case-series:²⁻⁴ drug
72 concentrations in the CSF have been described to be 3-7.8% of plasma ones even if a wide inter-
73 patient variability has been reported (with CSF-to-plasma ratios ranging from 0.01 to 0.61). In the
74 first report² altered blood-brain barrier (BBB) was associated with higherraltegravir cerebrospinal
75 fluid concentrations. Furthermore raltegravir has been proven to be p-glycoprotein and OAT1
76 substrate⁵ and both transporters are expressed at the blood brain barrier or at the CSF-blood barrier
77 (BCB).^{6,7} Furthermore Hepatocyte nuclear factor 4 alpha (HNF4 α), a zinc-finger protein, plays a
78 role in the transcriptional control of drug transporters: among the genes regulated by HNF4 α are a
79 broad range of xenobiotic-metabolizing cytochrome P450 iso-enzymes, UDP-
80 glucuronosyltransferases, sulfotransferases and transporters including organic anion transporter 2,
81 organic cation transporter 1, the ABC transporter ABCC2, ABCC6, ABCG5 and ABCG8.^{8,9} Recent
82 data have shown that both OAT1 (and OAT3) and HNF4 are expressed at the choroid plexus and
83 thus at the blood-CSF barrier.¹⁰

84 The primary objective of this study was to analyse the determinants of raltegravir cerebrospinal
85 fluid penetration including plasma concentrations, blood brain barrier damage, concomitant
86 antiretroviral drugs and single nucleotide polymorphisms (SNPs) in the genes encoding enzymes
87 present at the blood-brain barrier (*ABCB1*, *SLCO1A2*, *ABCC2*, *SLC22A6* and *HNF4*).

88

89 **Material and Methods**

90 Adults on stable raltegravir-based combination antiretroviral therapy (more than two weeks on
91 treatment) undergoing a lumbar puncture for clinical reasons were included. Patients signed a
92 written informed consent and this protocol was approved by the our Institution Ethics Committee.

93 Plasma and CSF raltegravir concentrations (2 to 15 hours after drug intake) were determined by
94 validated High Performance Liquid Chromatography coupled with photo diode array detection
95 (HPLC-PDA) and (modified for the CSF) Mass Spectrometry (HPLC-MS) methods,
96 respectively.^{11,12}

97 Trough concentrations were considered the ones collected after 10 to 14 hours after drug intake; less
98 than 30 minutes passed from CSF withdrawal to plasma sampling.

99 SNPs in selected genes were obtained through Real-time PCR [TaqMan Drug Metabolism
100 Genotyping Assays (Applied Biosystem)]. The eight SNPs selected were (1) ABCB1 (encodes P-
101 glycoprotein) 3435C→T (Ile1145Ile; rs1045642); 1236C→T (Gly412Gly; rs1128503); 2677G →
102 A/T (A:Ala893Thr, T:Ala893Ser; rs2032582), (2) SLCO1A2 (encodes OATP1A2) 38A→G
103 (Ile13Thr; rs10841795); 516A→C (Glu172Asp; rs11568563); (3) ABCC2 (encodes MRP-2) -
104 24G→A (in the promoter; rs717620); (4) SLC22A6 (encodes OAT1) 453G→A (in the 5' UTR,
105 rs4149170); (5) HNF4α (encodes HNF4α) 613C→G (in the promoter, rs1884613).

106 BBB damage was measured through Reibergram and measurement of albumin CSF to plasma ratios
107 (CSARs): normal values were considered below 6.5 below the age of 60 years and below 9.5 above
108 this age threshold.¹³

109 Baseline characteristics were tested for correlation to raltegravir CSF concentration and ratio by the
110 Spearman's test for continuous variables and by Mann-Whitney test for categorical variables.

111 Associations between genotypes and raltegravir CSF penetration were tested by univariate and
112 multivariate stepwise linear regression analyses: SNPs were categorized as dichotomous variables
113 according to the results of univariate analysis. The impact of other variables was estimated with
114 univariate analysis, and those with $P < 0.20$ were incorporated into multivariate analysis, in addition
115 to the basic demographics such as age and sex. Statistical significance was defined at 2-sided P

116 value <0.05 while for the effect of single SNPs a correction for multiple comparison defined a P
117 value <0.005. The online Hardy-Weinberg equilibrium calculator was used to test the selected
118 SNPs. (available at <http://www.oege.org/software/hwe-mr-calc.shtml>). All other statistical analyses
119 were performed with the Statistical Package for Social Sciences ver. 20.0 (IBM Corp. Released
120 2011. Armonk, NY: IBM Corp). Data are presented as medians (interquartile ranges).

121

122 **Results**

123 Forty-one patients (30, 73.2% male) were enrolled; median age and BMI were respectively 44 years
124 (39-50) and 20.9 kg/m² (18.7-22.7). Spinal taps were performed in patients with HIV-associated
125 neurological disorders [19, 46.3%; mostly neurological symptoms in the course of non CNS
126 opportunistic infections (10, 24.4%), HIV-associated neurocognitive disorders (6, 14.6%) and non
127 JCV-related leucoencephalopathy (3, 7.3%)], follow-up of opportunistic diseases [15, 36.6%; non-
128 Hodgkin's lymphomas (4, 9.7%), Burkitt's lymphoma (4, 9.7%), previous neurotoxoplasmosis (3,
129 7.3%), previous tubercular meningitis (2, 4.9%), previous cryptococcal meningitis (2, 4.9%)] or for
130 differential diagnosis of other clinical conditions (4, 9.7% such as seizures and hepatic
131 encephalopathy). Median CD4 cell count was 256 cells/uL (140-471), median plasma HIV RNA
132 level 1.76 log₁₀ copies/mL (1.28-2.61), and median CSF HIV RNA level 1.96 log₁₀ copies/mL
133 (1.28-2.95). The majority of patients presented concordant plasma and CSF viral loads: either both
134 below 20 copies/mL (13, 31.7%) or above 20 copies/mL (19, 46.3%); patients with neurological
135 complaints in the course of non CNS opportunistic infections had the highest plasma and CSF viral
136 loads (10 patients, 1947 copies/mL and 1117 copies/mL) while the remaining 31 subjects had HIV
137 RNA in both compartments below 1000 copies/mL.

138 Raltegravir was used in combination with different drugs in dual-regimens [with a boosted protease
139 inhibitor (PI), n=8], in three-drugs combination [n=15, mainly with two nucleos(t)ide reverse
140 transcriptase inhibitors (NRTI), n=7] or in intensified four-drugs treatments [n=18, associated with
141 2 NRTIs and a boosted PI (n=12) or a non-nucleoside reverse transcriptase inhibitor (n=6)].

CSF cells were absent in the majority of patients (38, 92,7%): one presented 7 cell/mL while two patients in the follow up of cryptococcal meningitis showed 40 and 60 cells/mL). Median CSF-serum albumin ratio (CSAR) was 5.6 (3.7-7.2) defining altered BBBs in 12 patients (29.2%). Patients with previous opportunistic infections had the highest prevalence of impaired BBB [10/15, 66.7% with median CSAR of 7 (6.2-8)].

CSF and plasma raltegravir concentrations were 31 ng/mL (21-56) (Fig. 1) and 165 ng/mL (83-552) accounting for 20.6% (3.8-36.3) of plasma drug concentrations.

In patients with trough determinations (n=35), CSF and plasma concentrations and CSF-to-plasma ratios (CPRs) were 32 ng/mL (21-57), 147 ng/mL (65-307) and 0.22 (0.12-0.47) respectively. Coefficients of variation for the three variables were 108%, 188% and 100%. Using recently published reference values¹⁴ no patient's concentration was below IC₅₀ (3.6 ng/mL), 25 (71.4%) were between IC₅₀ and IC₉₅ (44 ng/mL) and 10 (28.6%) were above IC₉₅.

CSF raltegravir concentrations correlated with plasma concentrations ($\rho=0.395$, $p=0.019$). Gender, age, BMI, time after drug intake and concomitant protease inhibitors in the regimen did not significantly influence raltegravir CSF levels and ratios (Spearman's correlations test). Although a direct correlation between raltegravir CPR and CSAR was not statistically significant ($\rho=0.306$, $p=0.10$) patients with BBB damage showed higher raltegravir CSF-to-plasma ratios [0.47 (0.23-1.13) versus 0.18 (0.06-0.29), $p=0.02$, Mann-Whitney] (Fig.2b) but not CSF concentrations [42 ng/mL (21-73) versus 30 ng/mL (20-43), $p=0.23$] (Fig.2a).

Data of single nucleotide polymorphisms prevalence and effect on trough CSF concentrations and CSF to plasma ratios are resumed in Table 1.

All polymorphisms were in Hardy-Weinberg equilibrium but the ABCB1 3435C→T and the ABCB1 2677G→A/T.

At multivariate linear regression analysis (including also raltegravir plasma concentrations and HNF4 α CG genotype with backward elimination) CSAR was the only independent predictor of raltegravir CSF concentrations (adjusted $R^2=0.61$, Beta=0.79, $P<0.001$, 95% CI 5.50-10.19). At

168 multivariate linear regression analysis CSAR was the only independent predictor of raltegravir CSF-
169 to-plasma ratios (adjusted $R^2=0.30$, Beta=0.57, P=0.001, 95% CI 0.02-0.06) with a non-significant
170 effect of HNF4 α CG genotype (Beta=-0.26, p=0.09, 95% CI -0.04+0.03).

171

172

173 Discussion

174 These data confirm the penetration of raltegravir in the cerebrospinal fluid although reporting
175 increased CSF to plasma ratios (22% versus the previously reported 3-8%). In the other studies the
176 percentage of patients with significant blood brain barrier impairment was not reported but a small
177 effect was noted in one of those: furthermore one patient with three samples showed a reduction
178 in raltegravir CPRs with the concomitant decrease in CSARs. This aspect suggests that CSF
179 pharmacokinetic studies should be performed in patients with different BBB and BCB permeability
180 since other drugs have shown a similar pattern¹⁵ but reporting the extent of BBB damage. The
181 clinical impact of such increased penetration is unclear since it may reflect higher total drug levels
182 bound to albumin or to other proteins present in the CSF.^{16,17} Furthermore a efficacy cut offs in the
183 CSF have not been validated: CSF and brain parenchyma levels can differ substantially although
184 drugs with higher neuropenetration/neuroefficacy have been associated with the decreased
185 likelihood of CSF viral replication.^{18,19} The report of all patients with CSF levels above the
186 published IC₅₀ suggests that the measured concentrations are potentially effective although we have
187 no data on the drug free fraction.

188 A linear correlation was noted between CSF and plasma concentrations as in the other papers.
189 Nevertheless at multivariate analysis the CSF to serum albumin ratio is the only independent factor
190 that partially explains the variability in CSF levels (60%) and in CSF penetration (30%). Being
191 blood brain barrier impairment quite common in the course of HIV infection²⁰ this could have
192 potential long-term effects: recently age and CSAR have been described as risk factors for the
193 development of HIV-associated Neurocognitive Disorders.²¹

194 Although SNPs in genes encoding enzymes involved in raltegravir transport (P-glycoprotein and
195 OAT1 and potentially OATP1A2 and MRP-2) at the BBB or BCB could potentially modulate drug
196 passage into the CSF, this study showed no such significant relationship. Furthermore it should be
197 noted that the precise effect of the different transporters present at the CNS barriers on CSF or
198 parenchyma drugs exposure is currently unclear. Anyhow, the effect of SNPs in the HNF4 α gene is
199 an interesting finding although multiple comparison may probably explain this results since after
200 Bonferroni correction it did not retain statistical significancy. This intra nuclear factor has been
201 described to regulate (along with PXR and CAR) several pathways and specifically the ones leading
202 to the expression of OAT1, OAT2 and OCT1.⁹ OAT1 is present at choroid plexus and has the
203 potential to regulate the passage of drugs at the blood CSF barrier¹⁰ and being raltegravir substrate
204 of this transporter a possible mechanism could be foreseen. Nevertheless with a limited samples
205 size and with ABCB1 polymorphisms not in Hardy-Weinberg equilibrium (possibly representing
206 population selection bias) we are not able to show clear effect of the studied SNPs. Furthermore the
207 co-administered drugs may potentially modulate drug transport at the BBB: while we found no
208 effect of protease inhibitors on raltegravir CSF penetration we had insufficient patients groups to
209 analyse other drugs influence (NNRTIs, NRTIs).

210 In conclusion, this study shows that raltegravir concentrations in the cerebrospinal fluid are above
211 the IC₅₀ in all studied patients with a very high inter-patient variability. Blood brain barrier
212 permeability is associated with raltegravir CSF concentrations and CSF-to-plasma ratios; larger
213 sample sizes are needed to fully investigate the effect on raltegravir neuropenetration of single
214 nucleotide polymorphisms in transporters-encoding genes.

215

216

217

218

219 **Funding:** This work was supported by internal funding.

220
221
222 **Transparency declaration:** A. Calcagno has received travel grants or speaker's honoraria from
223 Abbott, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD) and Janssen-Cilag; he is
224 currently receiving a research grant from Gilead. S. Bonora has received travel grants and
225 consultancy fees from Abbott, Boehringer-Ingelheim, BMS, Gilead-Sciences, GSK, MSD, Pfizer
226 and Janssen-Cilag; he is currently receiving a research grant from BMS. G. Di Perri has received
227 grants, travel grants and consultancy fees from Abbott, Boehringer-Ingelheim, BMS, Gilead-
228 Sciences, GSK, MSD, Pfizer, Roche and Tibotec (Johnson & Johnson). Other authors have no
229 potential conflict of interest to declare.

230
231
232
233

234 References

- 235
236 1. Rockstroh JK, Dejesus E, Lennox JL, *et al.* Durable Efficacy and Safety of Raltegravir
237 versus Efavirenz When Combined With Tenofovir/Emtricitabine In Treatment-Naive HIV-
238 1 Infected Patients: Final Five-Year Results From STARTMRK. *J Acquir Immune Defic Syndr.*
239 2013; **63**:77-85.
240 2. Yilmaz A, Gisslén M, Spudich S, *et al.* Raltegravir cerebrospinal fluid concentrations in HIV-1
241 infection. *PLoS One.* 2009; **4**:e6877.
242 3. Calcagno A, Bonora S, Bertucci R, *et al.* Raltegravir penetration in the cerebrospinal fluid of
243 HIV-positive patients. *AIDS.* 2010; **24**:931-2.
244 4. Croteau D, Letendre S, Best BM, *et al.* Total raltegravir concentrations in cerebrospinal fluid
245 exceed the 50-percent inhibitory concentration for wild-type HIV-1. *Antimicrob Agents*
246 *Chemother.* 2010; **54**:5156-60.
247 5. Moss DM, Kwan WS, Liptrott NJ, *et al.* Raltegravir is a substrate for SLC22A6: a putative
248 mechanism for the interaction between raltegravir and tenofovir. *Antimicrob Agents*
249 *Chemother.* 2011; **55**:879-87.
250 6. Sykes D, Sweet DH, Lowes S, *et al.* Organic anion transport in choroid plexus from wild-type
251 and organic anion transporter 3 (Slc22a8)-null mice. *Am J Physiol Renal Physiol.* 2004;
252 **286**:972-8.
253 7. Thuermer N, Fromm MF. The role of the transporter P-glycoprotein for disposition and effects
254 of centrally acting drugs and for the pathogenesis of CNS diseases. *Eur Arch Psychiatry Clin*
255 *Neurosci.* 2006; **256**:281-6.
256 8. Niehof M, Borlak J. Expression of HNF4alpha in the human and rat choroid plexus:
257 implications for drug transport across the blood-cerebrospinal-fluid (CSF) barrier. *BMC Mol*
258 *Biol.* 2009; **10**:68.
259 9. Ogasawara K, Terada T, Asaka J, *et al.* Hepatocyte nuclear factor-4{alpha} regulates the
260 human organic anion transporter 1 gene in the kidney. *Am J Physiol Renal Physiol.* 2007;
261 **292**:1819-26

10. Nagle MA, Wu W, Eraly SA, Nigam SK. Organic anion transport pathways in antiviral handling in choroid plexus in Oat1 (Slc22a6) and Oat3 (Slc22a8) deficient tissue. *Neurosci Lett*. 2013; **534**:133-8.
11. D'Avolio A, Baietto L, Siccardi M, *et al*. An HPLC-PDA method for the simultaneous quantification of the HIV integrase inhibitor raltegravir, the new nonnucleoside reverse transcriptase inhibitor etravirine, and 11 other antiretroviral agents in the plasma of HIV-infected patients. *Ther Drug Monit*. 2008; **30**:662-9.
12. D'Avolio A, Siccardi M, Sciandra M, *et al*. HPLC-MS method for the simultaneous quantification of the new HIV protease inhibitor darunavir, and 11 other antiretroviral agents in plasma of HIV-infected patients. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007; **859**:234-40. Erratum in: *J Chromatogr B Analyt Technol Biomed Life Sci*. 2008; **862**:265.
13. Tibbling G, Link H, Ohman S. Principles of albumin and IgG analyses in neurological disorders. I. Establishment of reference values. *Scand J Clin Lab Invest* 1977; **37**: 385–390.
14. Acosta EP, Limoli KL, Trinh L, *et al*. Novel method to assess antiretroviral target trough concentrations using in vitro susceptibility data. *Antimicrob Agents Chemother*. 2012; **56**:5938-45.
15. Calcagno A, Bonora S, Simiele M, *et al*. Tenofovir and emtricitabine cerebrospinal fluid-to-plasma ratios correlate to the extent of blood-brainbarrier damage. *AIDS*. 2011; **25**:1437-9.
16. Nguyen A, Rossi S, Croteau D, *et al*. Etravirine in CSF is highly protein bound. *J Antimicrob Chemother* 2013; **68**:1161-8.
17. Marchi N, Betto G, Fazio V, *et al*. Blood-brain barrier damage and brain penetration of antiepileptic drugs: role of serum proteins and brain edema. *Epilepsia*. 2009; **50**:664-77.
18. Letendre S, Ellis R, Deutsch R *et al*. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort. In *Abstracts from the Seventeenth Conference on Retroviruses and Opportunistic Infections*, 2010, San Francisco, USA. Abstract 430.
19. Giancola ML, Lorenzini P, Cingolani A, *et al*. Virological Response in Cerebrospinal Fluid to Antiretroviral Therapy in a Large Italian Cohort of HIV-Infected Patients with Neurological Disorders. *AIDS Res Treat*. 2012; **2012**:708456.
20. Abdulle S, Hagberg L, Gisslén M. Effects of antiretroviral treatment on blood-brain barrier integrity and intrathecal immunoglobulin production in neuroasymptomatic HIV-1-infected patients. *HIV Med*. 2005; **6**:164-9.
21. Letendre S, Croteau D, Ellis R, *et al*. Lower CSAR Are Associated with Global Neurocognitive Impairment in Antiretroviral-treated People with HIV. In *Abstracts from the Eighteenth Conference on Retroviruses and Opportunistic Infections*, 2011, Boston, USA. Abstract 408.

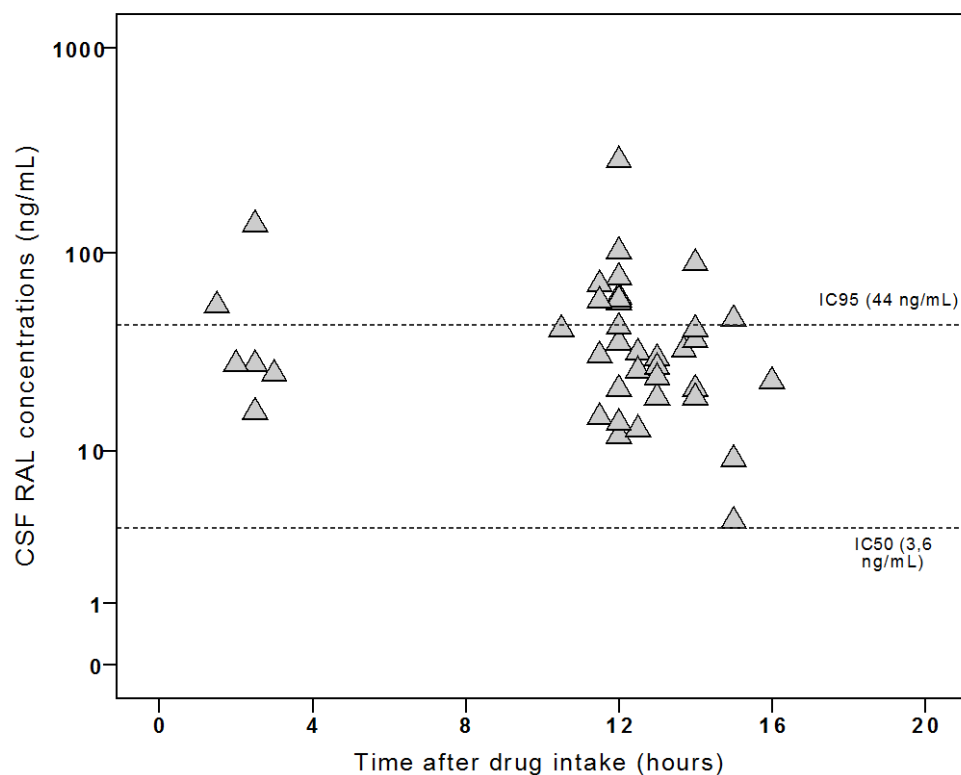


Figure 1. Raltegravir cerebrospinal fluid concentrations (Log_{10} ng/mL) according to time after drug intake (hours). Dotted lines represent IC_{50} and IC_{95} (in ng/mL).

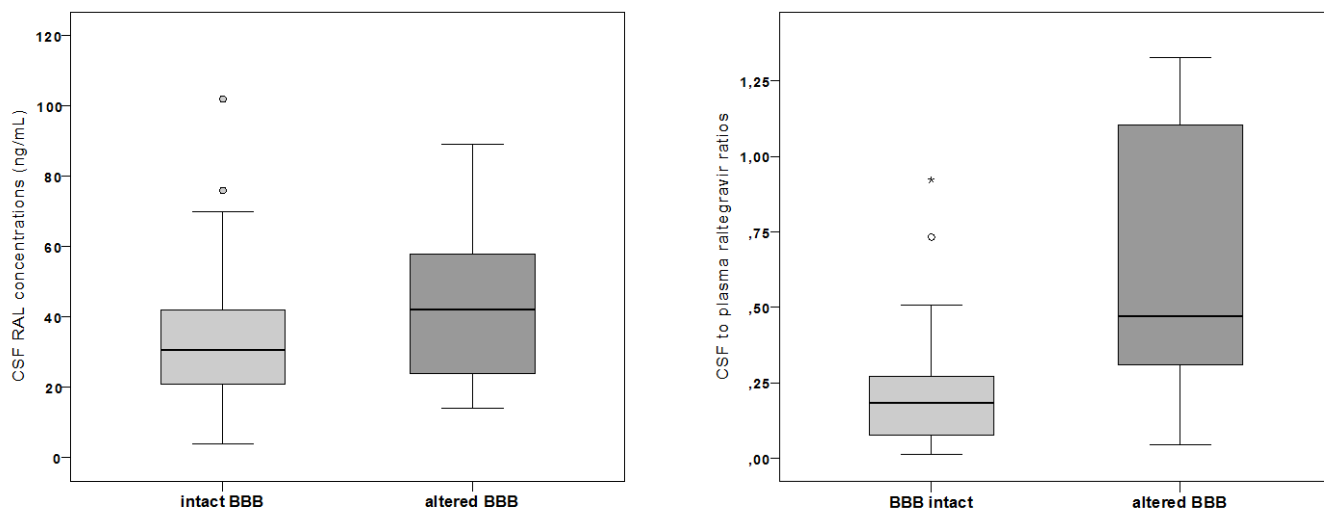


Figure 2. Raltegravir CSF concentrations (ng/mL, Figure 2a) and CSF-to-plasma ratios (Figure 2b) in patients with altered and intact blood brain barrier. Central lines and boxes represents medians and interquartile ranges; open circles and asterisks respectively represent outliers and extreme outliers.

genotype	n	CSF RAL conc	p value	CSF-P RAL ratio	p value
ABCB1					
3435C→T	rs1045642				
C/C	15	47 (19-70)		0.22 (0.12-0.50)	
C/T	8	26 (21-41)	0.40	0.23 (0.20-0.31)	0.97
T/T	12	31 (19-43)		0.24 (0.06-0.80)	
1236C→T	rs1128503				
C/C	14	32 (18-59)		0.21 (0.11-0.55)	
C/T	13	37 (22-56)	0.51	0.23 (0.14-0.32)	0.69
T/T	8	25 (16-40)		0.28 (0.07-1.05)	
2677G→A/T	rs2032582				
G/G	15	31 (19-59)		0.20 (0.07-0.50)	
G/A	1	102		0.17	
G/T	11	28 (21-42)	0.50	0.22 (0.22-0.31)	0.98
T/T	14	31(20-46)		0.17 (0.02-0.58)	
A/A	0	-		-	
SLC01A2					
38A→G	rs10841795				
A/A	25	32 (21-57)		0.27 (0.14-0.92)	
A/G	9	36 (20-56)	0.43	0.17 (0.07-0.35)	0.29
G/G	1	14		0.05	
516A→C	rs11568563				
A/A	34	31 (20-57)		0.22 (0.12-0.39)	
A/C	1	42	0.71	1.10	0.17
C/C	0	-		-	
ABCC2					
-24G→A	rs717620				
G/G	19	33 (23-47)		0.20 (0.13-0.47)	
G/A	15	30 (19-59)	0.40	0.27 (0.12-0.48)	0.42
A/A	1	14		0.05	
SLC22A6					
555G→A	rs4149170				
G/G	28	32.5 (21-59)		0.22 (0.11-0.44)	
G/A	6	30 (13-43)	0.50	0.20 (0.10-0.63)	0.92
A/A	1	21		0.19	
HNF4α					
4613X→Y	rs1884613				
C/C	25	37 (26-58)		0.27 (0.17-0.49)	
C/G	10	20 (15-29)	0.03	0.12 (0.04-0.24)	0.02
G/G	0	-		-	

Table 1. Genotype frequencies of different single nucleotide polymorphisms and their effect on Raltegravir cerebrospinal fluid concentrations (ng/mL) and CSF-to-plasma ratios. Abbreviations: n=number, conc=concentration